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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/887,540	06/21/2001	Robert Klein	R-193/40338.119USU1	5814

26619 7590 10/20/2005

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 10/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/887,540	KLEIN, ROBERT	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-19,24 and 26-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-19,24 and 26-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8-15-05 has been entered.

Claims 1-16, 20-23, 25 and 31 have been cancelled.

Claims 17-19, 24 and 26-30 remain pending and are under consideration in the instant office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant's arguments filed 8-15-05 have been fully considered but they are not persuasive.

The term "LPR5" in claims 26 and 30 has been changed to "LRP5" without the proper markings for an amendment. Please review all amendments for proper markings that indicate changes to the claims.

Specification

The amendment filed 1-28-05 remains objected to under 35 U.S.C. 132 because it introduced new matter into the disclosure. 35 U.S.C. 132 states that no amendment

shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The addition of the application numbers into paragraph 1 of pg 10 remains new matter. While US Patent Application 08/971,310 was converted to 60/084,194, and US Patent Application 09/885816 (US Patent 6,815,185) claims priority to 60/084,194, inclusion of Application number 09/885,816 and its parent applications (09/193934 and 60/084949) is new matter. Application 09/885816 is different than Application 08/971,310 and cannot be used to teach methods of preparing a targeting construct as newly amended in the first paragraph of pg 10. Amending the first sentence on pg 10 to "In a preferred embodiment of the present invention, the targeting construct is prepared directly from a plasmid genomic library using the methods described in pending U.S. Patent Application Ser. No.: 08/971,310, filed November 17, 1997, converted to provisional application 60/084,194" would overcome this objection.

Application number 09/954,483 added to pg 10, paragraph 2, on 1-28-05 is new matter. The original application number was 60/232,957. 60/232,957 was not marked in the amendment as being deleted, and 09/954,483 was not marked as being added. Please review all amendments to the specification for proper markings. The first sentence of paragraph two on pg 10 should be the same as the one originally filed.

Claim Rejections - 35 USC § 101

Claims 17-19, 24 and 26-30 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility for reasons of record.

Claims 17-19 and 26-30 are directed toward a transgenic mouse whose genome comprises a null allele of the endogenous low density lipoprotein related protein 5 (LRP5) allele.

> REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS repeated from http://www.uspto.gov/web/menu/utility.pdf
>
> "Specific Utility" - A utility that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.
>
> "Substantial utility" - a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material, which has a stated correlation to a predisposition to the onset of a particular disease condition, would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":
>
> A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.
>
> B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. 101.)
>
> C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility".

D. A method of making a material that itself has no specific, substantial, and credible utility.

E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

(Page 5-7 of utility guidelines).

A "well-known utility" is a specific, substantial and credible utility which is well know, immediately apparent, or implied by the specification's disclosure of the properties of the material, alone or taken with the knowledge of one skilled in the art. Neither a "well-established utility" nor a "specific utility" applies to any utility that one can dream up for an invention or a utility that would apply to virtually every member of a general class of materials, such as proteins or DNA.

(Paragraph bridging pg 32-33 of utility guidelines).

The knockout mice having retinal degeneration, increased anxiety or hypoactivity as described by applicants do not have a substantial utility because the abnormalities observed may have been a result of the mixed genome of the mice and not the disruption of the LRP5 gene itself. Applicants did not account for the mixed genome of the mice by providing evidence that the proper control mice of the same mixed genome were used.

Parson (Nature, Jan. 3, 2002, Vol. 415, pg 8-9) taught that the same knockout construct causes different phenotypes in different mouse strains (see entire article).

Crabbe of record (Science, June 4, 1999, Vol. 284, pg 1670-1672) specifically taught that the same knockout construct causes different neurobehavioral phenotypes in different mouse strains. Crabbe concludes that specific behavioral effects should not be uncritically attributed to genetic manipulations such as targeted gene deletions (pg 1672, col. 1, 2nd full ¶).

Lieter (Diabetologia, March 2002, Vol. 45, pg 296-308) discusses how the 129 genome of mixed strain 129-derived mice contributes to the metabolic phenotype of the mixed strain mice and points out that the phenotype may not be a result of the knockout itself (pg 298, "Strain 129: What do we know about glucose homeostasis in these mice?", see entire section). Lieter states the genetic environment must be standardized if the specific metabolic contribution of a mutation to diabetogenesis is to be separated from undefined strain background contributions" (pg 299, line 20-24). Lieter teaches that unexpected contributions of the 129 genome interacting deleteriously with the B6 genome caused researchers to revise their interpretation of the phenotype of β2m knockout mice (pg 300, col. 1, lines 10-15). Thus, Lieter taught that genetic background can greatly influence the diabetic nature (i.e. glucose metabolism) of transgenic mice and that care must be used in labeling a transgenic mouse as a model of diabetes.

Kulkarni (Diabetes, June 2003, Vol. 52, pg 1528-1534) taught that the genetic background of knockout mice impacts the phenotype of the mice in glucose and insulin tolerance test. Major differences in the metabolic phenotype occur when the same genetic mutation is introduced into three different strains of mice. Kulkarni concluded that backcrossing to various genetic backgrounds resulted in dramatic differences in glucose tolerance (¶ bridging col. 1-2 on pg 1528; pg 1528, col. 2, ¶ 3; pg 1532, col. 2, "Discussion"). Thus, the metabolic phenotype observed by applicants may be a result of the genetic background of the mice and not the genetic mutation itself and may be within the expected range for a mixed strain C57Bl/6 and 129/OslHsd mouse.

Kira (Neurosci. Letters, 2005, Vol. 384, pg 239-244) taught that metabolic

differences in knockout mice might stem from differences in genetic background because metabolic phenotypes are known to be very sensitive to the genetic background and environmental factors.

The knockout mice described by applicants have mixed genomes, which would be 25% 129/OlaHsd genotype and 75% C57Bl/6. Given the teachings in the art, applicants must compare the knockout mice to other mice having the same mixed genome to properly account for the variability of phenotypes between different mouse strains. While the specification teaches using the mice in tests and comparing them to controls, the specification does not teach what type of control was used (pg 3, lines 21-24; pg 14, lines 23-25; pg 18, lines 24-28 and pg 19, lines 16-21). The specification broadly states any "animal without a disruption of the LRP5 gene, e.g. wild-type mouse" can be used as a control. Without showing the knockout mice were compared to controls that were of equivalent mixed strain or that the wild-type phenotypes of C57Bl/6 and 129/Ola/Hsd were the same for the phenotype being tested, one of skill would not be able to conclude that the observed difference was attributed to the knockout of LRP5 gene and not the 129/OlaHsd genotype of the F2 mice.

Therefore, the mice claimed do not have substantial utility because the retinal degeneration, increased anxiety or hypoactivity observed may have been a result of the mixed genome of the mice and not the disruption of the LRP5 gene itself and because applicants did not account for the mixed genome of the mice by using the proper control mice of the same mixed genome.

Furthermore, the phenotypes observed in the mice described by applicant may be a result of other genes compensating for the disruption of LRP5.

Scarff (genesis, 2003, Vol. 36, pg 149-157) taught the phenotype of knockout mice may be a result of the retention of the selectable marker gene in the mice, which affects expression of neighboring genes, i.e. the observed phenotype may not be a result of the disruption of the gene itself.

> "It is becoming apparent that retention of the selectable marker gene in knockout mice can lead to a confounding phenotype. In most cases the retained selectable marker gene affects the expression of neighbouring genes."
> (pg 155, col. 1, 2nd full ¶).

Pham (PNAS, Nov. 1996, Vol. 93, pg 13090-13095) taught the phenotype of a knockout mouse might be due to disruption of neighboring genes within the same locus as the target gene and the disruption of the target gene itself (see abstract).

Olsen of record (GABA in the Nervous System, 2000, pg 81-95) taught that "although gene targeting is often useful in delineating the contribution of a given gene product to phenotypic characteristics observed, some gene knockouts lead to embryonic or perinatal lethality, and others lead to no apparent phenotype. This can arise from a lack of any role for the gene in question in regard to the trait studies or from compensation by other gene products. Analysis of the compensation can yield valuable clues to the genetic pathway" (pg 82, last 11 lines of col. 1).

Srivastava (PNAS, Nov. 23, 1999, Vol. 96, No. 24, pg 13783-13788) taught making an ANX7 -/- mouse with defects in insulin secretion and that the observed phenotype was a result of compensation by making more secreting cells and loading each secretory granule with more insulin (pg 13788, last full ¶).

Thus, the abnormal phenotype observed by applicant may not be due to the disruption in LRP5 itself. As such, mice with a decreased glucose tolerance as claimed do not have a specific utility because the phenotype may not be specific to the disruption in the LRP5 gene.

Overall, the mice claimed do not correlate to gas chromatographs, screening assays and nucleotide sequencing methods having specific, credible and substantial utilities. Gas chromatographs separate the chemical components of a compound and identify them. Screening assays have various functions, but may be used, for example, to determine the amount of protein expression in a population of cells. Sequencing methods provide the nucleotide sequence of a nucleic acid molecule. Unlike gas chromatographs, screening assays or sequencing methods, the mice claimed are capable of providing data, but the may not reveal the function of the gene or provide any substantially useful information. For example, applicants used the mice of the invention in expression, phenotypic and behavioral analyses without determining the function of the LRP5 gene, correlating the phenotype to a disease or identifying agents that alter the phenotype of the mice capable of treating disease. Further research would be required to determine the function of the LRP5 gene, how to use the mouse as a model of eye disease, anxiety or activity disorders or to identify agents capable of treating disease. The utility guidelines state using a product for further research is not a "substantial" utility. In this case, the expression analysis and phenotype analyses merely provide a clue that the LRP5 gene is related to retinal degeneration, anxiety and hypoactivity. Therefore, using the mouse claimed as a research tool, specifically for

expression and phenotype analyses, does not provide any substantial utility.

Using the mice to identify agents capable of altering a phenotype would require further research and is not a "substantial utility" or "specific utility." Bowery of record (Pharm. Rev., 2002, Vol. 54, pg 247-264) taught, "no unique pharmacological or functional properties have been assigned to either subunit or the variants" of $GABA_B$. "The emergence of high-affinity antagonists for $GABA_B$ receptors has enabled a synaptic role to be established. However, than antagonists have generally failed to establish the existence of pharmacologically distinct receptor types within the $GABA_B$ receptor class. The advent of $GABA_{B1}$ knockout mice has also failed to provide support for multiple receptor types" (pg 247, col. 2, lines 4-). Thus, knockout mice may be used to identify agents that bind to the knocked out gene ($GABA_B$ in the case of Bowery or lipoprotein-related protein 5 in the instant application), but the agent may not treat disease or ameliorate any symptom of disease. Further research would be required to determine how to use such an agent identified using the mouse, which is not a "substantial utility" (see Utility Guidelines for examples of things that do not have "substantial utility" "C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility"). Using the mice to identify agents capable of altering a phenotype is also not a "specific utility" because the agent may be affecting other proteins in the pathway and not LPR5 itself. Using the mice to identify agents capable of altering a phenotype is also not a "specific utility" because the agent may be found using wild-type mice.

Olsen and Bowery also show that knockout mice do not necessarily reveal the function of the knocked out gene. Neither reference used the mice to determine the function of the knocked out gene. Significant further research would be required to do so because no blaze marks for determining the genes' function using the mice have been set forth.

The specification teaches making LRP5 -/- mice (pg 50). The specification suggests using the mice to test compounds for neurological, neuropsychological or psychotic disease, but the specification does not disclose one specific neurological, neuropsychological or psychotic disease in humans linked to a disruption in LRP5 (pg 19, lines 8-11). The mice were tested in "open field testing" (Fig. 4 and 5 and pg 51); however, the results of the open field test do not correlate to a useful phenotype because "possible increased anxiety" and "significant hypoactivity" (lines 4 and 7 of pg 51) are not specific to any disease and are not statistically significant because the number of mice tested is not disclosed and the difference observed is not significant. In fact, it cannot be determined what the "2,1," means in "2,1, -/-, Male" or "2,1, +/+, Male" in Fig. 4 and 5. The mice also had retinal degeneration. The specification suggests using the mice as a model of disease relating to disruptions in LRP5 (pg 19, lines 4-6). The mice claimed cannot be used to determine compounds that modulate LRP5 expression because LRP5 is not expressed in the mice. Using the mice to determining whether a particular phenotype is ameliorated is not a specific or substantial utility because the specification does not link the phenotype to any specific disease or to a disease caused by a disruption in humans. The specification does not identify any

compounds that alter neurological, neuropsychological, or psychotic phenotypes using the mice. Thus, the specification does not provide a specific or substantial use for a mouse having retinal degeneration, increased anxiety or hypoactivity as claimed.

Significant further research would be required to use the mice to determine the function of the LRP5 gene because applicants have not set forth any blaze marks for determining the genes' function using the mice. Applicants have tested the mice in assays but did not determine the function of the LRP5 gene. Nowhere does the specification provide any blaze marks for one of skill in the art to determine the function of the LRP5 gene using the mice. In fact, the mice may never reveal the function of LRP5. Therefore, the mice do not have utility for determining the function of LRP5.

Since the time of filing, LRP5 disruptions have been linked to osteoporosis-pseudoglioma syndrome (OPPG) in humans (Gong of record, 11-16-01, Cell, Vol. 107, pg 513-523, abstract), which is not taught or suggested in the instant application. A mouse having a homozygous disruption in LRP5 having features of osteoporosis-pseudoglioma syndrome has been made since the time of filing (Kato, of record, J. Cell Biology, 2002, Vol.1 57, pg 303-314; abstract and pg 304, col. 2, "Generation of Lrp5-/- mice"), which is not taught or suggested in the instant application. Thus, the specification does not provide the essential blaze marks for one of skill to determine how the mice are linked to human disease.

The MPEP and utility guidelines clearly set forth that a "well-established utility" must be specific, substantial and credible. While knockout mice were used for scientific research in the art at the time of filing, significant further

research was required to determine the function of the gene. In fact, the function of the gene may never be determined from the knockout mouse. A mouse requiring significant further research to determine the function of the gene does not rise to the level of having a "well-established utility." Using the mouse for further research is not a substantial utility, which is specifically described in the utility guidelines:

> [T]he following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":
>
> A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

In this case, further study of mice would have been required to determine how to use the mouse of applicants' invention as a model of eye disease, anxiety or hypoactivity. As such, using the mice claimed to determine whether the mice are models of disease is not a "substantial utility."

Specifically, claims 17 and 19 require the mouse has hypoactivity. A mouse having hypoactivity as claimed does not have a patentable utility because:

i) Hypoactivity is defined as abnormally decreased motor and cognitive activity, with slowing of thought, speech and movement. Hypoactivity is generic to numerous medical conditions, such as depression and aging. While hypoactivity can be a symptom of a medical condition, hypoactivity can be secondary to medical conditions, i.e. recovery from surgery, the flu, allergies, or can be a symptom of non-medical

conditions, i.e. changing jobs from being a construction worker to working behind a desk, laziness, driving to work instead of walking. A mouse that is slower than average in an open filed test does not represent all types of hypoactivity or one particular type of hypoactivity;

ii) Applicants' conclusion in the Example, that a mouse that has a slower velocity represents hypoactivity in an open field test, is unfounded. Applicants' conclusion does not take into account possible physiological conditions that may have caused the slower velocity related to bone or muscle structure/function. Mice having a slow velocity do not correlate directly to all forms of hypoactivity. Mice with a slower velocity than wild-type mice are slower than wild-type mice; that is all that can be concluded from such a study.

iii) Using a mouse having hypoactivity to determine drugs that increase activity is not a specific or substantial utility because wild-type animals can also be used to determine drugs that increase activity.

Similarly, claims 17 and 18 require the mouse has increased anxiety as determined by a decrease in time spent in a central region of an open field test. A mouse that spends less time in the central region of an open field test may not have anxiety as claimed because the mouse may have decreased mobility due to a muscular or neural dysfunction. One of skill cannot definitively conclude the LRP5 knockout mice were anxious. Even the specification acknowledges the results indicate "possible increased anxiety". However, the specification does not provide the blaze marks for one of skill to conclude the results indicate the LRP5 gene is linked to anxiety.

Applicants argue the claimed invention has a well-established utility because a person of ordinary skill would immediately appreciate why the knockout mice were useful to determine the function of a gene. Applicants' argument is not persuasive. No evidence of such a "well-established use" has been provided. The examiner has provided evidence of knockout mice that provided clues as to the function of a knocked out gene without providing the function of the gene. Merely providing a clue to the function of a gene without providing the function of the gene within the pathway or generic area does not rise to the level of a specific or substantial utility – an essential feature used to define "well-established" utilities (see MPEP 2701 II(A)(3)). Furthermore, the specification does not contemplate using the mice to determine the function of the LRP5 gene.

Applicants argue the mice have substantial utility because they can be used to study gene function. While knockout mice were used "to study gene function" at the time of filing, significant further research was required to determine the function of the gene using the mouse. In fact, the function of the gene may never be determined from the knockout mouse. Olsen of record (GABA in the Nervous System, 2000, pg 81-95) taught that "although gene targeting is often useful in delineating the contribution of a given gene product to phenotypic characteristics observed, some gene knockouts lead to embryonic or perinatal lethality, and others lead to no apparent phenotype. This can arise from a lack of any role for the gene in question in regard to the trait studies or from compensation by other gene products. Analysis of the compensation can yield valuable

clues to the genetic pathway" (pg 82, last 11 lines of col. 1). Using the mouse "to study gene function" without determining the gene function does not rise to the level of a substantial utility. The utility guidelines clearly state "Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved" is not a substantial utility. In this case, further study may never reveal the function of the LRP5 gene and significant further study would be required to do so. Applicants have not provided the blaze marks for further study so that one of skill would determine the function of the LRP5 gene using the mouse. As such, the mice do not have substantial utility to determine the function of LRP5.

Applicants argue the mice have substantial utility because they indicate the LRP5 gene is involved in retinal degeneration, increased anxiety and hypoactivity. The mouse claimed does not have a substantial use in the patentable sense because it does not teach the function of LRP5 within the realm of retinal degeneration, increased anxiety and hypoactivity. Merely using the LRP5 knockout mice to obtain a clue that the LRP5 gene is involved in retinal degeneration, anxiety and hypoactivity is not a substantial use for the mice. The mice are not models of retinal degeneration, anxiety or hypoactivity because retinal degeneration, anxiety and hypoactivity have not been linked to LRP5 disruptions in humans with retinal degeneration, anxiety or hypoactivity. The combination of phenotypes does not correlate to any disease condition. In particular, it is unclear how a mouse with increased anxiety also having decreased activity is a model of any disease. Overall, applicants have not provided the blaze marks for further study so that one of skill would use the mouse claimed to determine the function of the

LRP5 gene within the realm of retinal degeneration, increased anxiety and hypoactivity. As such, the mouse claimed does not have substantial utility to determine the function of LRP5 within the realm of retinal degeneration, increased anxiety and hypoactivity.

Applicants argue the mouse claimed has specific utility because the mouse can be used to study the association of the LRP5 gene with retinal degeneration, anxiety or hypoactivity. Applicants' argument is not persuasive. Nowhere does the specification teach how to perform such further investigation. Nor can such further investigation be envisioned. Overall, applicants have not provided the blaze marks for further study so that one of skill would use the mouse claimed to determine the function of the LRP5 gene within the realm of retinal degeneration, increased anxiety and hypoactivity. Furthermore, the phenotype may not be specific to the disruption of the LRP5 gene because other proteins may compensate for the loss of LRP5 and result in the observed phenotypes (Olsen of record). Drugs identified using the mouse that change the phenotype may not be specific to the LRP5 protein because the drugs may affect other proteins in the LRP5-related pathway to change the phenotype. As such, the mouse claimed does not have specific utility to determine the function of LRP5 within the realm of retinal degeneration, increased anxiety and hypoactivity.

Applicants cite en re Brana and state the mice meet the legal principle of en re Brana because mice having retinal degeneration, for example, can be used as a model of eye disease. Applicants conclude that if it is well known to those skilled in the art that knockout mice are useful for studying gene function, then those skilled in the art would certainly regard such use as credible, specific and substantial. Applicants'

arguments are not persuasive. First, only claims 17-19 are limited to mice with a phenotype. Second, mice with hypoactivity in claims 17 and 19 do not correlate to any diseases. Third, it is not clear that the disruption in LRP5 caused the retinal degeneration, anxiety or hypoactivity. Fourth, it is not clear that humans with retinal degeneration, anxiety or hypoactivity have a disruption the LRP5 gene. Fifth, applicants have not provided any evidence indicating the mice will reveal the function of LRP5, specifically within the realm of retinal degeneration, anxiety or hypoactivity. Sixth, applicants analysis of en re Brana ignores the lack of substantial or specific utility cited by the examiner. Seventh, any wild-type mouse can be used to determine whether the LRP5 gene is associated with retinal degeneration, i.e. LRP5 expression in the retina of wild-type mice can be determined, particular old mice in which retinal degeneration occurs. The examiner has provided ample reasoning and evidence why those of skill in the art at the time of filing would not recognize how to use the LRP5 knockout mice to determine the association of the LRP5 gene with retinal degeneration, anxiety or hypoactivity. Significant further research in this case would be required to use the LRP5 mice to determine the association of the LRP5 gene with retinal degeneration, anxiety or hypoactivity. Therefore, using the mice claimed to determine the "association" of the LRP5 gene with retinal degeneration, anxiety or hypoactivity does not constitute a patentable utility because the use is not a specific or substantial utility.

Applicants argue the issue is not whether the asserted utility is specific for a disease but whether the asserted use is specific for the claimed invention. Applicants'

argument is not persuasive. The asserted utility is not specific to the claimed invention because any mouse having retinal degeneration can be used to determine whether the LRP5 gene is associated with retinal degeneration. Furthermore, using the mouse as a model for retinal degeneration is so general as to be meaningless. The asserted use of using the mice to determine the association of the LRP5 gene with retinal degeneration, anxiety or hypoactivity is merely a starting point for further research not the end point of any research effort.

Applicants argue Austin and the NIH report can be used to establish utility despite being filed after the filing date of the instant application. Applicants argue the specification clearly sets forth using the mice claimed for determining gene function. Applicants' argument is not persuasive. Nowhere does the specification assert the mice can be used to determine gene function. The examiner has provided evidence indicating the mice may not capable of determining gene function. Applicants assert Austin and the NIH report were not cited to support a post-filing assertion of utility but applicants fail to correlate the teachings of Austin or the NIH report to the asserted utilities in the specification originally filed. While en re Brana considered a declaration regarding utility filed after the original filing date, the utility described in the declaration correlated to the specification as originally filed and showed the asserted specific and substantial utility was indeed true. In this case, applicants have not provided any evidence, specifically Austin and the NIH report, indicating the LRP5 knockout mice will reveal the association of the LRP5 gene with retinal degeneration, anxiety or hypoactivity or the function of the LRP5 gene.

Applicants argue Doetschman provides utility for the mice claimed. Applicants' argument is not persuasive. Doetschman taught that the phenotype may be caused by the mixed background of the knockout mice and not be caused by the knockout (¶ bridging pg 28-29). Doetschman does not teach that every mouse with a disruption will reveal the function of the disrupted gene. The knockout mice described by Doetschman merely provide clues as to the disrupted gene's function similar to the clues obtained in the instant application. However, significant further investigation would be required to determine the function of a gene using the mouse described by Doetschman or by applicants.

Applicants request for evidence that 129/OlaHsd wild-type mice exhibit retinal degeneration is moot. The examiner has i) provided evidence that a number of phenotypes, including anxiety, of mouse strains vary, ii) provided scientific reasons why a mixed breed mouse being compared to a pure bred strain of mouse, and iii) asserted that applicants did not use the proper control to determine the phenotypes of the knockout mice. No specific evidence indicating that the rate of retinal degeneration in 129/OlaHsd and C57Bl6 mice varies. Applicants have not provided any evidence that 129/OlaHsd and C57Bl6 mice have the same rate of retinal degeneration, anxiety or activity or that the proper equivalent mixed breed strain of mouse was used as a control.

Applicants argue that one of skill would have understood that mice of the same background were used to determine the phenotype of the knockout mice. Applicants cite pg 19 and argue that "wild-type control mice" is a standard term used and refers to a strain, age, and gender-matched mouse. Applicants' argument is not persuasive. Pg

19 of the specification merely indicates that wild-type mice were used and does not indicate the mice were non-transgenic littermates of the knockout mice or that the mice were of an equivalent mixed breed. Pg 3, lines 21, 24, pg 14, lines 23-25, pg 18, lines 24-28, and pg 19, lines 16-21 are generic to using any wild-type mouse as a control. Pg 19, lines 19-21, specifically states any "animal without a disruption in the LRP5 gene, e.g. wild-type mouse" is encompassed by the phrase. One of skill would not have recognized that applicants used mice without a disruption in the LRP5 gene from the same litter as the homozygous knockout mice.

Applicants argue LRP5 has since been linked to retinal and eye disorders in humans (Jiao, of record, Am. J. Human Gen., 2004, Vol. 75, No. 5, pg 878-884). Applicants' argument is not persuasive. The specification did not provide the blaze marks for one of skill to perform the further study described by Jiao or to determine that familial exudative vitreoretinopathy (FEVR) described by Jiao was linked to a disruption in the LRP5 gene using the mice described in the specification. In addition, FEVR comprises vitreous detachment, vitreous membranes, heterotopia of macula, retinal detachment, neovascularization, and recurrent haemorrhage (definition of exudative vitreoretinopathy from On-line Medical Dictionary), which is greater than just having retinal degeneration. Applicants examined the eye of the mouse but did not teach the eye had vitreous detachment, vitreous membranes, heterotopia of macula, retinal detachment, neovascularization, and recurrent haemorrhage. Furthermore, retinal detachment is a species of retinal degeneration as claimed and was not

taught in the specification as originally filed. Finally, Jiao was not available at the time of filing. Therefore, Jiao cannot be used to provide post-filing evidence for the asserted utility of using the mouse as a model of eye disease because the specification did not reveal the mice had the specific symptoms of FEVR or provide the blaze marks to lead those of skill to consider using the mice as a model for FEVR.

Applicants' arguments ignore Gong and Kato, both of record, who taught LRP5 disruptions were linked to osteoporosis-pseudoglioma syndrome in humans. Applicants do not teach or suggest the mice had osteoporosis-pseudoglioma syndrome or that the LRP5 gene was linked to osteoporosis-pseudoglioma syndrome.

Applicant's arguments ignore the lack of correlation between decreased distance traveled in an open field test and "hypoactivity" asserted by the examiner, i.e. the decreased distance traveled may have been a result of a muscular or neural dysfunction and not "hypoactivity" as claimed.

Claim Rejections - 35 USC § 112

Enablement

Claims 17-19, 24 and 27-30 remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above,

one skilled in the art clearly would not know how to use mice having retinal degeneration, increased anxiety or hypoactivity for reasons of record.

Applicants argue the claimed invention is enabled for reasons set forth above. Applicants' argument is not persuasive for reasons set forth above.

Claims 17, 24 and 26 are rejected because the specification does not provide a nexus between the disruption in LRP5 and the phenotypes of retinal degeneration, increased anxiety or hypoactivity. Applicants have not addressed this portion of the rejection.

Claim 24 is directed toward a method of making a transgenic mouse having a disruption in an LRP5 gene using a mouse embryonic stem cell having a disruption in an LRP5 gene, introducing the ES cell into a mouse blastocyst, implanting the blastocyst into a pseudopregnant mouse which gives birth to chimeric mice, and breeding the chimeric mouse to produce the transgenic mouse. A pseudopregnant mouse (a condition resembling pregnancy) cannot give birth to a chimeric mouse as claimed until the mouse becomes pregnant (contains unborn young within the body).

Claim 26 requires a mouse with a null allele of the LRP5 gene. The phrase "null allele" was known in the art and was described by Hasty as "to ablate the function of a target gene (null allele)" (see Hasty, 1999, provided by applicants). Thus, claim 26 encompasses a mouse without a functional LRP5 gene. Example 1 taught disrupting the gene by homologous recombination using a "construct having the ability to disrupt or modify genes" (pg 50, lines 2-7); however, nowhere does the specification teach the construct ablates the function of the LRP5 gene in the knockout mouse. Without

evidence to the contrary, it is not readily apparent that the construct ablated function of the LRP5 gene because the specification contemplated numerous other types of disruption (pg 6, lines 16-22).

New matter

Claims 17-19, 24 and 26-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection regarding "comprising exogenous DNA" in claim 26 has been withdrawn because the phrase "comprising exogenous DNA" has been deleted.

The phrase "positive selection marker" in claim 27 as newly amended has support on pg 7, line 1.

The rejection regarding the limitation of "PGK-neo fusion gene having two lacO sites" in claim 29 has been withdrawn. Support is found on pg 10, lines 14-19.

The phrase "null allele" in claims 17, 26 and 27 remains new matter. Applicants argue the term was known in the art as described by Hasty who taught "to ablate the function of a target gene (null allele)." Thus, applicants argue the phrase "null allele was limited to a gene in which the function has been ablated. Applicants point to Example 1 which taught disrupting the gene by homologous recombination using a "construct having the ability to disrupt or modify genes" (pg 50, lines 2-7). Applicants'

arguments are not persuasive. Nowhere does the specification teach the construct ablates the function of the LRP5 gene in the knockout mouse.

The phrase "endogenous" in claim 26 is new matter. No support has been provided and none can be found in the specification as originally filed.

Indefiniteness

Claims 17-19, 24 and 26-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "LRP5 gene" is definite. The phrase "LRP5 gene" is defined in the specification as "a comprising [sic] SEQ ID NO: 1 or comprising the sequence identified in Genebank as Accession No. NM_008513; G1:6678715. In one aspect, the coding sequence of the LPR5 gene comprises SEQ ID NO: 1 or comprises the gene identified in Genebank as Accession No. NM_008513; G1:6678715" (pg 6, lines 11-15). The phrase "LRP5 gene" encompasses SEQ ID NO: 1 or the sequence identified in Genebank as Accession No. NM_008513; G1:6678715.

The phrase "null allele" in claims 17, 26 and 27 is indefinite. An allele is defined as "one of a variant form of a gene at a particular locus, or location on a chromosome. Different alleles produce variation in inherited characteristics such as hairy color or blood type" (definition of "allele" from genome.gov). "Null allele" can be defined as ablating the function of a target gene (Hasty (2000), cited by applicants) OR "an allele

whose effect is either an absence of normal gene product at the molecular level or an absence of normal function at the phenotypic level (Genetics Glossary definition of "null allele", last updated "19/11/97"; see attached). It is unclear that applicants intended the phrase to be limited to a disruption that ablates gene function as defined by Hasty because other definitions of "null allele" existed and because the specification contemplated a whole host of disruptions (pg 6, lines 16-23). Without such guidance, one of skill would not have known that "null allele" was intended to be limited to the definition of Hasty. Overall, applicants did not provide adequate guidance for one of skill to determine which definition known in the art to use to define the metes and bounds of "null allele".

Claim 24 is indefinite because "pseudopregnant" mice do not give birth. The pseudopregnant mouse becomes pregnant before giving birth. Therefore, use of the term "pseudopregnant" to describe a mouse that gives birth is a misnomer because the pseudopregnant mouse is only pseudopregnant before the embryo is implanted into her uterus.

Claim 28 is indefinite because "said gene" may refer to either the "gene encoding a positive selection marker" or the "LRP5 gene."

Claim 29 is indefinite because "said exogenous DNA" is no longer in parent claim 26.

Claim 30 is indefinite because "LRP5 allele" is no longer in parent claim 26.

Claim Rejections - 35 USC § 102

The rejection of claims 24, 26-28 and 30 under 35 U.S.C. 102(b) as being anticipated by Rohlmann (Nature Biotech., Nov. 1996, Vol. 14, pg 1562-1565) or Rohlmann (1998, J. Clin. Invest., Vol. 101, pg 689-695) has been withdrawn.

Rohlmann (1996) taught making a transgenic mouse having a disruption in LRP using a construct with the neo gene inserted into the LRP gene transfected into ES cells (pg 1652, col. 2, "Generation of $LRP^{flox/flox}$"; pg 1653, col. 2, Fig. 1A). The patent office does not have the ability to analyze the mouse described by Rohlmann to determine how the LRP gene disrupted by Rohlmann correlates to the LRP5 gene claimed. Therefore, without evidence to the contrary, the LRP gene disrupted by Rohlmann was inherently the LRP5 gene as claimed because it had the same structure as SEQ ID NO: 1 or comprised SEQ ID NO: 1 and encoded SEQ ID NO: 2.

Rohlmann (1998) also described the mouse made by Rohlmann in 1996.

Rohlmann (1996) and Rohlmann (1998) did not teach the genome of the mouse had a null allele of the LRP5 gene as claimed. The reference taught that only the liver cells had a null allele of the LRP5 gene, not the entire genome of the mouse as claimed.

Claim Rejections - 35 USC § 103

The rejection of claims 24, 26-28 and 30 under 35 U.S.C. 103(a) as being unpatentable over Rohlmann (Nature Biotech., Nov. 1996, Vol. 14, pg 1562-1565) in view of Hey (1998, Gene, Vol. 216, pg 103-111) has been withdrawn.

Rohlmann (1996) taught making a transgenic mouse having a disruption in LRP using a construct with the neo gene inserted into the LRP gene transfected into ES cells (pg 1652, col. 2, "Generation of $LRP^{flox/flox}$"; pg 1653, col. 2, Fig. 1A). Rohlmann did not teach the LRP gene encoded for the amino acid sequence of SEQ ID NO: 2.

Rohlmann (1996) did not teach the genome of the mouse had a null allele of the LRP5 gene as claimed. Rohlmann taught that only the liver cells had a null allele of the LRP5 gene, not the entire genome of the mouse as claimed.

Claims 24 and 26-30 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Signorini (1997, PNAS, Vol. 94, pg 923-927) in view of Hey (1998, Gene, Vol. 216, pg 103-111) for reasons of record.

Signorini taught making a transgenic mouse having a heterozygous or homozygous disruption in an inward rectifier protein (GIRK2/Kir3.2). The disruption comprised DNA cassette encoding PGK and neomycin which was visible using PCR (pg 924, col. 2, 2nd ¶; caption to Fig. 1 on pg 924). Signorini did not teach disrupting the LRP5 gene in the mice.

However, Hey taught the nucleic acid sequence encoding SEQ ID NO:2.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make a transgenic mouse having a disruption in a protein as taught by Signorini wherein the protein was LRP5 as taught by Hey. One of ordinary skill in the art at the time the invention was made would have been motivated to disrupt the LRP5 gene instead of the Kir3.2 gene to determine the function of LRP5 *in vivo*.

Applicants argue the references combined are not enabling to produce the claimed mouse because the references do not teach the genomic sequence of the LRP5 gene. Applicants' argument is not persuasive. One of ordinary skill in the art would have had a reasonable expectation of successfully making an ES cell with a disruption of a LRP5 gene using the cDNA of Hey because methods of making knockout mice using the cDNA were known in the art. Smart (Neuron, April 1998, Vol. 20, pg 809-819), Scrocchi (Nature Med., Nov. 1996, Vol. 2, No. 11, pg 1254-1258) and Varfolomeev (Immunity, Aug. 1998, Vol. 9, pg 267-286) used cDNA to isolate genomic sequence of a gene and how to make a targeting construct using the genomic sequence, map the gene and construct a targeting vector using that information (Scrocchi, pg 1257, col. 2, "Targeting vector;" Varfolomeev, pg 273, last 4 lines, through pg 274, col. 2, line 7). Thus, Smart, Scrocchi and Varfolomeev support the fact that it was well within the knowledge of those of ordinary skill in the art at the time of filing to use the cDNA of Hey to isolate genomic sequence of the LRP5 gene and make the mouse claimed. Applicants have not provided any reason why the cDNA of Hey could not be used to isolate the genomic sequence of the LRP5 gene using the methods known in the art described for example by Smart, Scrocchi and Varfolomeev.

Applicants' argument that Hey is limited to the LRP5 protein of SEQ ID NO: 2 is moot because Hey taught GenBank accession number AF064984, the nucleic acid sequence encoding SEQ ID NO: 2.

Conclusion

The prior art made of record and not relied upon remain pertinent to applicant's disclosure.

Weaver of record (J. Biol. Chem., May 30, 1997, Vol. 272, No. 22, pg 14372-14379) taught cells with a deletion in LRP but did not teach mice with a deletion in LRP.

Kim of record (J. Biochem., 1998, Vol. 124, pg 1072-1076) described the human and rabbit LRP5 genes, which was expressed in the liver.

Pinson of record (Nature, Sept. 28, 2000, Vol. 407, pg 535-538) made a transgenic mouse having a disruption in LRP6 using a trap vector transfected into ES cells (pg 538, col. 1, 1st full ¶). The LRP6 gene described by Pinson is not an LRP5 gene as claimed because it is not a variant form of the LRP5 gene at the LRP5 locus on the chromosome. While LRP6 may have homology with LRP5, LRP6 is not an LRP5 gene as claimed.

Fujino of record (PNAS, Jan. 7, 2003, Vol. 100, No. 1, pg 229-234).

Jiao of record (Am. J. Human. Genetics, 2004, Vol. 75, pg 878-884).

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

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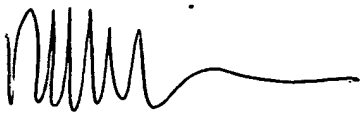
Michael C. Wilson



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